Benefits of Tadalafil and Sildenafil on Mortality, Cardiovascular Disease, and Dementia

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Running Head: Benefits of Tadalafil and Sildenafil

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D.V.J., K.K.P., and H.J. were involved in the conception, methodology design, and conduct of the study and the analysis and interpretation of the results. R.S., H.U., and A.A.J. wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. D.V.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest: None

Abstract

Background: Erectile dysfunction and lower urinary tract symptoms, from benign prostatic hyperplasia and bladder neck obstructions, are prevalent in men and associated with an increased risk of cardiovascular diseases. Phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil and sildenafil, are used to treat erectile dysfunction and may also offer cardiovascular benefits due to their vasodilatory effects. This study evaluates the impact of these PDE-5 inhibitors on all-cause mortality, cardiovascular disease, and dementia in middle-aged men with erectile dysfunction and lower urinary tract symptoms over a 3 year follow-up period.

Methods: This longitudinal study analyzed data from 50 million US men using the TriNetX database. Men at least 40 years of age prescribed tadalafil or sildenafil after an erectile dysfunction diagnosis, or tadalafil after lower urinary tract symptom diagnoses, from 2004 to 2021 were included. Three-year outcomes assessed included all-cause mortality, cardiovascular disease, and dementia, comparing men on PDE-5 inhibitors to those not on these medications. Propensity matching was performed for demographics and eight pre-existing conditions.

Results: The final cohort included 509,788 men with erectile dysfunction and 1,075,908 with lower urinary tract symptoms. Tadalafil and sildenafil were associated with significantly reduced risks of all-cause mortality (RR 0.66/0.76), myocardial infarction (0.73/0.83), stroke (0.66/0.78), venous thromboembolism (0.79/0.80), and dementia (0.68/0.75) in erectile dysfunction patients, with tadalafil showing more significant benefits. In lower urinary tract symptom patients, tadalafil was similarly associated with reduced mortality, cardiovascular disease, and dementia.

Conclusions: In conclusion, tadalafil and sildenafil use in erectile dysfunction patients reduced mortality, cardiovascular disease, and dementia risks, with tadalafil providing more benefits. Tadalafil also conferred similar benefits to patients with lower urinary tract symptoms.

Introductions

Cardiovascular diseases, including myocardial infarctions, and strokes, are major causes of mortality in the United States[1]. The development of these conditions is influenced by a combination of environmental, genetic, and lifestyle factors. Erectile dysfunction and lower urinary tract symptoms have both been linked to an increased risk of cardiovascular disease[2,3]. Effective management of these conditions is crucial for reducing morbidity and mortality[4].

Phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil and sildenafil, have emerged as potential therapeutic agents for cardiovascular disease due to their ability to inhibit the degradation of cGMP in smooth muscle, leading to relaxation and improved blood flow[5]. They are believed to offer cardiovascular benefits through vasodilation, enhanced endothelial function, and improved sexual activity[5,6]. These medications are FDA-approved for treating erectile dysfunction, idiopathic pulmonary hypertension, and lower urinary tract symptoms associated with benign prostatic hyperplasia[6].

Research has explored the cardiovascular benefits of PDE-5 inhibitors, with several smaller studies indicating that these medications may reduce cardiovascular complications and mortality in patients with erectile dysfunction[7,8]. However, many of these studies focused on specific populations, such as those with type 2 diabetes[8]. Retrospective longitudinal analyses have suggested that PDE-5 inhibitors may lower the incidence of major adverse cardiovascular events (MACE), mortality, and venous thromboembolisms; however, no clear comparisons between doses were assessed[7,9,10]. Evidence from animal models and retrospective studies also hints at cognitive benefits, but large-scale clinical trials are lacking[11,12].

This longitudinal study aims to evaluate the effects of tadalafil and sildenafil on all-cause mortality, and the development of myocardial infarction, cerebrovascular accidents (stroke),

venous thromboembolism, and dementia over a 3 year follow-up period using a large, real-world database.

Methods

Data collection and analysis for this study was performed retrospectively using the TriNetX database, a global health research network that is both HIPAA and GDPR-compliant[13]. The US Collaborative Network within the TriNetX platform was utilized, which consisted of 62 healthcare organizations (HCOs) including large academic medical institutions, specialty physicians' services, and community hospitals to provide de-identified EMR data (diagnoses, procedures, medications, and laboratory values) of over 50 million male patients within the United States.

Cohort Definition

Cohorts were developed within the TriNetX database to compare patient populations using ICD-10 codes. A primary analysis was conducted of men at least 40 years old with erectile dysfunction (ICD10:N52) without a history of cardiovascular disease (**Figure 1**) who were given any dose of tadalafil (RXNORM:358263) without other PDE-5 inhibitors within 6 months on or after the diagnosis compared to a similar group who were not given any PDE-5 inhibitors. The study period was between February 22, 2004, to February 22, 2021. PDE-5 inhibitors were defined as tadalafil, avanafil (RXNORM:1291301), vardenafil (RXNORM:306674), or sildenafil (RXNORM:13641). Cardiovascular disease was defined as patients with a diagnosis of acute myocardial infarction (ICD10:I21), heart failure (ICD10:I50), cerebral infarction (ICD10:I63), or unstable angina (ICD10:I20.0).

The same cohorts were compared for patients who received tadalafil 5 mg (RXNORM:358263) within 6 months on or after the diagnosis of erectile dysfunction without any other PDE-5 inhibitors. The comparison with tadalafil 5 mg was chosen as this is often utilized in chronic therapy versus as-needed treatment for the higher doses. Another analysis was performed to compare patients who received any dosage of sildenafil within 6 months on or after the diagnosis of erectile dysfunction versus the same patient population who did not receive any PDE-5 inhibitors. Patients given avanafil, vardenafil, or tadalafil were excluded from this sildenafil analysis to avoid confounding. A sub-group analysis was performed comparing any dose of tadalafil without any other PDE-5 inhibitors versus any dose of sildenafil without any other PDE-5 inhibitors.

Secondary Analysis with Lower Urinary Tract Symptoms

A secondary analysis was conducted to compare men at least 40 years old with lower urinary tract symptoms without a history of cardiovascular disease who were given any dosage of tadalafil within 6 months on or after the diagnosis compared to the same population not given any PDE-5 inhibitors. The same cohorts were again compared for patients who received tadalafil 5 mg within 6 months on or after the diagnosis of lower urinary tract symptoms without any other PDE-5 inhibitors. Lower urinary tract symptoms was defined as patients with a diagnosis of obstructive and reflux uropathy (ICD10:N13), overactive bladder (ICD10:N32.81), benign prostatic hyperplasia with lower urinary tract symptoms (ICD10:N40.1), nodular prostate with lower urinary tract symptoms (ICD10:N40.3), pain associated with micturition (ICD10:R30), vesical tenesmus (ICD10:R30.1), frequency of micturition (ICD10:R35.0), nocturia (ICD10:R35.1), other and unspecified symptoms and signs involving the genitourinary system

(ICD10:R39), feeling of incomplete bladder emptying (ICD10:R39.14), or straining to void (ICD10:R39.16). Patients given avanafil, vardenafil, or sildenafil were excluded from this secondary analysis.

A post-hoc analysis was done to evaluate the impact of socioeconomic status and potential confounders related to affordability and accessibility for the prescriptions of Tadalafil at all dosages and outcomes in patients with erectile dysfunction or lower urinary tract symptoms. Tadalafil is fairly affordable at present, although initially, it was moderately expensive. This post-hoc analysis was performed to ensure that prescriptions for tadalafil did not just represent higher socioeconomic status. The presence of the ICD-10-codes Z56.0 (Unemployment, unspecified) or Z59 (Problems related to housing and economic circumstances) was used as a marker for lower socioeconomic status and was evaluated for the tadalafil group.

Outcomes

We examined 5 outcomes in this study including all-cause mortality, myocardial infarction (ICD10:I21), stroke (ICD10:I63), venous thromboembolism (ICD10:I82), and dementia (ICD10:F02 and ICD10:F03). Cardiovascular outcomes were defined as myocardial infarction, stroke, and venous thromboembolism. The outcomes were measured from the day of the index event to 3 years after the index event.

Statistical Analysis

A 1:1 propensity score matching was done with linear regression for continuous variables and logistic regression for binary outcomes for each analysis. Patients were matched for the following pre-existing diseases: diabetes mellitus (ICD10:E08-E13), acute kidney failure and

chronic kidney disease (ICD10:N17-N19), overweight and obesity (ICD10:E66), cardiac arrest (ICD10:I46), ischemic heart diseases (ICD10:I20-I25), malignant neoplasm of bronchus and lung (ICD10:C34), COPD (ICD10:J44), and hypertension (ICD10:I10-I16). Greedy nearest-neighbor matching was utilized as described in Supplementary Appendix, Page 3. This study methodology has been previously validated[13,14]. Comparisons were made between cohorts before and after propensity matching for both the primary (erectile dysfunction) and secondary (lower urinary tract symptoms) analysis. After propensity matching, all of the standard mean differences of the covariates were less than 0.1, indicating a well-balanced match.

Univariate analysis with chi-square and t-test was performed in TriNetX on February 22, 2024, for each cohort, reported as descriptive statistics, risk ratios (RRs), 95% confidence intervals (CIs) of these ratios, and probability values (p-values). Utilization of the data from TriNetX does not require UTMB IRB review as this is an analysis of de-identified data and is considered “not human subjects research”.

Results

A total of 3,781,305 male patients with erectile dysfunction or lower urinary tract symptoms were identified from 2004 to 2021. After exclusions, 1,625,932 patients 40 years and older with either condition were analyzed. For erectile dysfunction, 81,179 patients (15.9%) received tadalafil, 20,597 (25.4% of all dosages) of whom received tadalafil 5 mg. Additionally, 184,523 patients (36.2%) received sildenafil, and 244,086 (47.9%) received no PDE-5 inhibitors. For lower urinary tract symptoms, 37,383 patients (3.5%) received tadalafil, with 13,704 (36.7% of all dosages) receiving tadalafil 5 mg. The remaining 1,024,821 patients (96.5%) did not any receive PDE-5 inhibitors (**Figure 1, Table 1**).

Tadalafil versus No PDE-5 Inhibitors in Erectile Dysfunction

Patients with erectile dysfunction who received tadalafil showed reduced all-cause mortality, improved cardiovascular outcomes, and lower rates of dementia compared to those who did not receive any PDE-5 inhibitors. These findings were consistent before and after propensity matching. Tadalafil 5 mg also demonstrated significant improvements in these outcomes (**Table 2**).

Sildenafil versus No PDE-5 Inhibitors in Erectile Dysfunction

Sildenafil use in erectile dysfunction patients was associated with reductions in all-cause mortality, cardiovascular events, and dementia. These results were significant both before and after propensity matching (**Table 2**).

Tadalafil versus Sildenafil in Erectile Dysfunction

Tadalafil was associated with significantly lower rates of all-cause mortality (RR 0.87), myocardial infarction (RR 0.87), and stroke (RR 0.85) compared to sildenafil. Rates of venous thromboembolism (RR 1.00, p=0.96) and dementia (RR 0.89, p=0.13) were similar between tadalafil and sildenafil (**Table 2**).

Tadalafil versus No PDE-5 Inhibitors in Lower Urinary Tract Symptoms

Tadalafil use in lower urinary tract symptoms patients was linked to lower all-cause mortality, better cardiovascular outcomes, and reduced dementia rates compared to those who

did not receive any PDE-5 inhibitors. This trend was consistent both before and after propensity matching. Tadalafil 5 mg also showed significant improvements in these outcomes (**Table 2**).

Post-hoc Analysis of Socioeconomic Status

The post-hoc analysis showed that patients prescribed tadalafil were slightly less likely to be unemployed or face housing and economic issues compared to those not prescribed PDE-5 inhibitors, showing relative risks that varied by only 1-4%. This factor had minimal impact on the primary analysis results.

Discussion

In this study, it was shown that men aged 40 years and older with erectile dysfunction prescribed tadalafil experienced significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia, compared to those not using PDE-5 inhibitors. Similarly, sildenafil also showed significant reductions in these outcomes. Tadalafil was particularly associated with better cardiovascular outcomes than sildenafil, with statistical significance confirmed both before and after propensity matching.

A secondary analysis of men aged 40 years and older with lower urinary tract symptoms but without cardiovascular disease within five years of lower urinary tract symptoms incidence revealed that tadalafil 5 mg daily resulted in significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia compared to no PDE-5 inhibitor treatment. These results align with previous reviews, which noted an independent association between tadalafil and major adverse cardiovascular events (MACE), showing benefits in all-cause mortality and reduced venous thromboembolism risk[10].

Tadalafil's recommended dosage ranges from 5 mg to 20 mg daily, and clinical practice often involves titration to balance efficacy and side effects. A recent cohort study of 48,692 men with erectile dysfunction and high cardiovascular risk noted a dose-dependent reduction in overall mortality and MACE. This supports our findings that chronic daily tadalafil (5 mg) is at least as effective as as-needed doses[9].

Tadalafil may be more effective than sildenafil due to its longer half-life (17.5 hours in healthy men and up to 21.6 hours in elderly men) compared to sildenafil's approximately 4 hours. This extended therapeutic window and daily dosing could explain why tadalafil is favored in this study[15]. This corresponds to a therapeutic window of tadalafil of approximately 36 hours. In addition, tadalafil is often prescribed as a daily dose both for erectile dysfunction and for lower urinary tract symptoms. The continuous mechanism of action of tadalafil over time may be a reason why the data in this study favors tadalafil over sildenafil. Tadalafil may also serve as an adjunct for treatment-resistant hypertension in males with a concomitant diagnosis of erectile dysfunction. This synergistic effects with other antihypertensives, can serve to benefit select patients from a mortality and vascular disease perspective[16], as seen in this study.

Initially investigated for hypertension and angina, PDE-5 inhibitors are now known to cause erections as a side effect[17]. They have also been explored for managing angina, heart failure, stroke, and lower urinary tract symptoms. Previous studies have reported significant reductions in unstable angina, heart failure, stroke, and mortality with PDE-5 inhibitors[7,9,10,18]. Our study confirms these findings and adds that PDE-5 inhibitors also reduce all-cause mortality, myocardial infarction, stroke, and venous thromboembolism, while expanding their role in dementia.

PDE5 inhibitors have anti-aggregatory effects and increase in cGMP which may ameliorate small vessel dysfunction in the systemic and pulmonary circulation[5,6]. Outside of their cardiovascular uses mentioned above, PDE-5 inhibitors have additional uses. Literature has shown PDE-5 inhibitors to reduce hypoxic pulmonary hypertension which could aid in high-altitude illnesses[19,20]. A 2021 review article supported the nephroprotective roles of PDE-5 inhibitors in animal-based models through changes in molecular compounds affecting kidney functioning[21]. Other research has also been done studying their effects on neuropathy and fertility[22,23].

Sildenafil and tadalafil are noteworthy in that they can cross the blood-brain barrier, as PDE-5 enzymes are expressed in brain neurons as well as subcortical white matter cells. Given this, PDE-5 inhibition may play a role in the modulation of vasodilatory responses in the CNS, decreasing the risk of dementia and Alzheimer's disease[11]. Animal models with PDE5 inhibitors have demonstrated improvement in memory deficits after 10 weeks of treatment as well as decreased tau phosphorylation after 10 weeks of treatment; however, a change was not demonstrated in amyloid beta levels in transgenic mice[24]. The results of this study show promise in favor of this information, demonstrating a statistically significant reduction in dementia diagnoses in the subgroup with erectile dysfunction treated with tadalafil and sildenafil versus no treatment. In addition, PDE5 inhibitors may act to release hydrogen sulfide, the deficiency of which has been implicated in the vascular hypothesis of dementia[25,26].

A study conducted in the United Kingdom found similar results as this study, showing an 18% lower risk of Alzheimer's dementia in men greater than or equal to 40 years of age using any PDE-5 inhibitors compared to non-users, with sildenafil showing significant risk reduction in those over 70 with diabetes or hypertension[27]. Furthermore, individuals prescribed greater than

20 prescriptions were typically associated with a reduced risk of Alzheimer's dementia[27]. Future research should explore the effects of less commonly prescribed PDE-5 inhibitors, such as vardenafil and avanafil, on erectile dysfunction and lower urinary tract symptoms as more data becomes available.

Strengths and Limitations

The strengths of this study include the large cohort size, which is significantly larger than those in prior studies, the use of propensity matching to control for confounders, the utilization of data from a large, real-world database encompassing healthcare organizations across the US, and the practical implications of using relatively inexpensive medications to reduce mortality, improve cardiovascular outcomes, and lower the risk of dementia. The follow up for mortality is excellent in this database, as 94% of sites are linked to the death registries in the US. The follow up for the other outcomes could be missing if an individual sought subsequent healthcare outside of the HCOs and this is a potential limitation of this study.

This retrospective database review from multiple HCOs establishes correlations but cannot infer causality. While propensity matching accounted for diabetes mellitus, kidney failure, obesity, cardiac conditions, malignancies, COPD, and hypertension, other diseases and socioeconomic factors may not have been fully controlled. The TriNetX database has limitations in capturing comprehensive demographic factors and pre-existing conditions, which may affect the findings.

Socioeconomic factors, such as Medicaid coverage limitations on lifestyle drugs, could influence medication affordability[28]. Our post hoc analysis suggests these factors have minimal impact with only a 1-4% difference in relative risks. The study does not address side effects like headaches, flushing, angina, or priapism, and we cannot determine if medications were

discontinued due to these effects. Additionally, since both tadalafil and sildenafil are processed by the CYP450 system, interactions with other medications or dietary supplements could confound results[29].

TriNetX, relying on EHR and insurance claim data, may have misclassification bias. The database does not track patient compliance with medications, which is crucial for chronic therapies like tadalafil. There is also uncertainty about whether tadalafil 5 mg was used as intended for chronic therapy.

The study focused on males due to FDA approval and prescription guidelines for erectile dysfunction and lower urinary tract symptoms. However, off-label use in females exists, suggesting potential cardioprotective benefits for them as well. Future research should explore outcomes such as all-cause mortality, myocardial infarction, stroke, and venous thromboembolism risk in females prescribed tadalafil.

Conclusion

Males 40 years of age and older with erectile dysfunction taking tadalafil experienced significant reductions in all-cause mortality, myocardial infarction, stroke, venous thromboembolism, and dementia compared to those not on the medication. Both tadalafil and sildenafil provided benefits, with tadalafil showing more favorable outcomes. In patients with lower urinary tract symptoms, tadalafil also demonstrated significant benefits. In the clinical treatment of patients, 5 mg daily dosing of tadalafil should be considered for all individuals with erectile dysfunction, or lower urinary tract symptoms. Further research is needed to explore the effects of low-dose tadalafil in patients with cardiovascular diseases and dementia risk, and

randomized controlled trials should be conducted to establish causation between PDE-5 inhibitors and reductions in mortality, cardiovascular diseases, and dementia.

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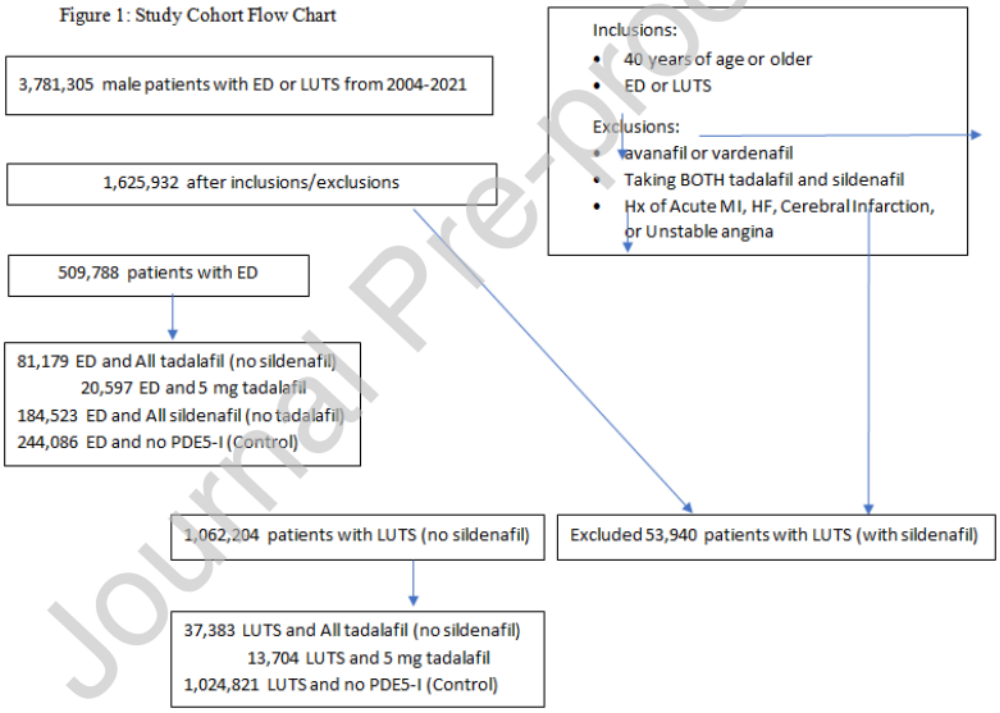
Figure 1: Study Cohort Flow Chart



Running Head: Benefits of Tadalafil and Sildenafil

Tables

Table 1: Study Characteristics of Tadalafil All Dosages (n=81,179) Versus No PDE5-Inhibitors (n=244,086) in Erectile Dysfunction Patients

		Before Propensity Score Matching					After Propensity Score Matching				
Demographics											
Cohort		Mean±SD	Patients	% of Cohort	P-Value	Std diff.	Mean±SD	Patients	% of Cohort	P-Value	Std diff.
1† 2‡	Age at Index	58.4±9.6 60.3±10.3	81,143 235,478	100% 100%	<0.001*	0.194	58.4±9.6 58.4±9.6	81,138 81,138	100% 100%	=0.66	0.002
1 2	White		57,017 163,696	70.3% 69.5%	<0.001*	0.016		57,017 57,330	70.3% 70.7%	=0.09	0.008
1 2	American Indian or Alaska Native		196 580	0.2% 0.2%	=0.81	0.001		196 163	0.2% 0.2%	=0.08	0.009
1 2	Unknown Race		8,688 24,091	10.7% 10.2%	<0.001*	0.016		8,683 8,518	10.7% 10.5%	=0.18	0.007
1 2	Native Hawaiian or Other Pacific Islander		105 473	0.1% 0.2%	<0.001*	0.018		105 108	0.1% 0.1%	=0.84	0.001
1 2	Unknown Ethnicity		19,810 57,547	24.4% 24.4%	=0.89	0.001		19,810 19,976	24.4% 24.6%	=0.34	0.005
1 2	Not Hispanic or Latino		57,326 161,899	70.6% 68.8%	<0.001*	0.041		57,321 57,195	70.6% 70.5%	=0.49	0.003
1 2	Hispanic or Latino		4,007 16,032	4.9% 6.8%	<0.001*	0.080		4,007 3,967	4.9% 4.9%	=0.65	0.002
1 2	Black or African American		10,880 34,048	13.4% 14.5%	<0.001*	0.030		10,880 10,911	13.4% 13.4%	=0.82	0.001
1 2	Other Race		2,748 8,244	3.4% 3.5%	=0.13	0.006		2,748 2,632	3.4% 3.2%	=0.11	0.008
1 2	Asian		1,509 4,346	1.9% 1.8%	=0.80	0.001		1,509 1,476	1.9% 1.8%	=0.54	0.003
Diagnosis											
Cohort		Mean±SD	Patients	% of Cohort	P-Value	Std diff.	Mean±SD	Patients	% of Cohort	P-Value	Std diff.
1 2	Diabetes mellitus		12,974 37,935	16.0% 16.1%	=0.42	0.003		12,974 13,063	16.0% 16.1%	=0.55	0.003
1 2	Acute kidney failure and chronic kidney disease		4,086 12,128	5.0% 5.2%	=0.20	0.005		4,086 4,000	5.0% 4.9%	=0.33	0.005
1 2	Overweight and obesity		10,969 23,723	13.5% 10.1%	<0.001*	0.107		10,964 10,803	13.5% 13.3%	=0.24	0.006
1 2	Cardiac arrest		33 129	0.0% 0.1%	=0.13	0.006		33 21	0.0% 0.0%	=0.10	0.008
1 2	Ischemic heart diseases		5,909 18,547	7.3% 7.9%	<0.001*	0.022		5,909 5,858	7.3% 7.2%	=0.63	0.002
1 2	Malignant neoplasm of bronchus and lung		223 842	0.3% 0.4%	<0.001*	0.015		223 181	0.3% 0.2%	=0.04*	0.010
1 2	Other chronic obstructive pulmonary disease		2,160 7,348	2.7% 3.1%	<0.001*	0.027		2,160 2,066	2.7% 2.5%	=0.14	0.007
1 2	Hypertensive diseases		33,326 79,249	41.1% 33.7%	<0.001*	0.154		33,321 33,446	41.1% 41.2%	=0.53	0.003

PDE5, Phosphodiesterase Type-5; SD, Standard Deviance; Std diff., Standard Difference; †Cohort 1 = History of Erectile Dysfunction and Tadalafil All Dosages; ‡Cohort 2, History of Erectile Dysfunction and No PDE5-inhibitors; *Statistically significant

Table 2: Mortality, Cardiovascular, and Dementia Outcomes Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
2a: Erectile Dysfunction Cohort						
Outcomes	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	1,576 (1.95%)	7,623 (3.25%)	0.60 (0.57,0.63)	1,576 (1.95%)	2,379 (2.94%)	0.66 (0.62,0.71)
MI	736 (0.91%)	3,101 (1.32%)	0.69 (0.64,0.75)	736 (0.91%)	1,014 (1.25%)	0.73 (0.66,0.80)
Stroke	655 (0.81%)	2,979 (1.27%)	0.64 (0.59,0.69)	655 (0.81%)	993 (1.22%)	0.66 (0.60,0.73)
VTE	1,003 (1.26%)	3,810 (1.64%)	0.77 (0.72,0.82)	1,003 (1.26%)	1,279 (1.60%)	0.79 (0.72,0.85)
Dementia	342 (0.42%)	1,973 (0.84%)	0.50 (0.45,0.56)	342 (0.42%)	502 (0.62%)	0.68 (0.59,0.78)
Outcomes	**Tadalafil 5mg (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil 5mg (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	369 (1.80%)	7,623 (3.25%)	0.55 (0.50,0.61)	369 (1.80%)	596 (2.90%)	0.62 (0.55,0.70)
MI	194 (0.94%)	3,101 (1.32%)	0.72 (0.62,0.83)	194 (0.94%)	289 (1.40%)	0.67 (0.56,0.80)
Stroke	172 (0.84%)	2,979 (1.27%)	0.66 (0.57,0.77)	172 (0.84%)	242 (1.18%)	0.71 (0.59,0.86)
VTE	269 (1.33%)	3,810 (1.64%)	0.81 (0.72,0.92)	269 (1.33%)	365 (1.80%)	0.74 (0.63,0.86)
Dementia	93 (0.45%)	1,973 (0.84%)	0.54 (0.44,0.66)	93 (0.45%)	134 (0.65%)	0.69 (0.53,0.90)
Outcomes	**Sildenafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Sildenafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	4,334 (2.43%)	7,627 (3.25%)	0.75 (0.72,0.77)	3,999 (2.42%)	5,241 (3.17%)	0.76 (0.73,0.80)
MI	2,072 (1.16%)	3,098 (1.32%)	0.88 (0.83,0.93)	1,890 (1.14%)	2,274 (1.37%)	0.83 (0.78,0.88)
Stroke	1,822 (1.02%)	2,977 (1.26%)	0.80 (0.76,0.85)	1,693 (1.02%)	2,181 (1.31%)	0.78 (0.73,0.83)
VTE	2,378 (1.35%)	3,811 (1.64%)	0.82 (0.78,0.87)	2,188 (1.34%)	2,746 (1.68%)	0.80 (0.76,0.84)
Dementia	885 (0.50%)	1,974 (0.84%)	0.59 (0.54,0.64)	857 (0.52%)	1,140 (0.69%)	0.75 (0.69,0.82)
Outcomes	**Tadalafil All (%)**	**Sildenafil All (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**Sildenafil All (%)**	**RR (95% CI)**
Deceased	1,577 (1.95%)	4,334 (2.43%)	0.80 (0.76,0.85)	1,577 (1.95%)	1,805 (2.23%)	0.87 (0.82,0.93)
MI	738 (0.91%)	2,072 (1.16%)	0.79 (0.72,0.86)	738 (0.91%)	846 (1.04%)	0.87 (0.79,0.96)
Stroke	655 (0.81%)	1,822 (1.02%)	0.79 (0.73,0.87)	655 (0.81%)	772 (0.95%)	0.85 (0.77,0.94)
VTE	1,005 (1.26%)	2,378 (1.35%)	0.93 (0.87,1.00)	1,005 (1.26%)	1,007 (1.26%)	1.00 (0.92,1.09)
Dementia	342 (0.42%)	885 (0.50%)	0.85 (0.75,0.97)	342 (0.42%)	383 (0.47%)	0.89 (0.77,1.03)
2b: Lower Urinary Tract Symptom Cohort						
Outcomes	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil All (%)**	**No PDE5i (%)**	**RR (95% CI)**

Deceased	953 (2.56%)	64,512 (6.42%)	0.40 (0.37,0.43)	953 (2.56%)	2,175 (5.84%)	0.44 (0.41,0.47)
MI	312 (0.83%)	13,322 (1.32%)	0.63 (0.57,0.71)	312 (0.83%)	498 (1.33%)	0.63 (0.54,0.72)
Stroke	294 (0.79%)	12,497 (1.24%)	0.64 (0.57,0.71)	294 (0.79%)	456 (1.22%)	0.65 (0.56,0.75)
VTE	609 (1.66%)	23,402 (2.36%)	0.70 (0.65,0.76)	609 (1.66%)	898 (2.45%)	0.68 (0.61,0.75)
Dementia	231 (0.62%)	18,316 (1.83%)	0.34 (0.30,0.39)	231 (0.62%)	511 (1.38%)	0.45 (0.39,0.53)
Outcomes	**Tadalafil 5mg (%)**	**No PDE5i (%)**	**RR (95% CI)**	**Tadalafil 5mg (%)**	**No PDE5i (%)**	**RR (95% CI)**
Deceased	337 (2.47%)	64,512 (6.42%)	0.38 (0.35,0.43)	337 (2.47%)	867 (6.35%)	0.39 (0.34,0.44)
MI	128 (0.93%)	13,322 (1.32%)	0.71 (0.59,0.84)	128 (0.93%)	180 (1.31%)	0.71 (0.57,0.89)
Stroke	106 (0.77%)	12,497 (1.24%)	0.62 (0.52,0.76)	106 (0.77%)	181 (1.32%)	0.59 (0.46,0.74)
VTE	231 (1.72%)	23,402 (2.36%)	0.73 (0.64,0.83)	231 (1.72%)	363 (2.71%)	0.64 (0.54,0.75)
Dementia	94 (0.69%)	18,316 (1.83%)	0.38 (0.31,0.46)	94 (0.69%)	181 (1.33%)	0.52 (0.40,0.66)

PDE5i, Phosphodiesterase Type 5 Inhibitor; RR, Relative Risk; CI, Confidence Interval; MI, Myocardial Infarction; VTE, Venous Thromboembolism; *Control Outcome; Outcomes were within 3-years of diagnosis of ED or LUTS.

Clinical Significance:

- Tadalafil and Sildenafil are increasingly being prescribed for erectile dysfunction and lower urinary tract symptoms.
- Tadalafil and Sildenafil are associated with lower all-cause mortality, myocardial infarction, cerebral vascular accidents, venous thromboembolism, and dementia.
- Tadalafil is associated with significantly more cardiovascular benefits compared to Sildenafil in erectile dysfunction patients.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: